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**Research Article**

# ANALYSIS OF TREATMENT OUTCOME IN CERVIX CANCER PATIENTS TREATED WITH CO-60 HDR BRACHYTHERAPY: AN INSTITUTIONAL EXPERIENCE AT TERTIARY CARE CENTRE IN NORTH WEST INDIA

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**A R T I C L E I N F O**

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**A B S T R A C T**

**Introduction:** In India, cervical cancer accounts for almost 14% of all female cancer cases and second most common cancer in females. In past, Iridium-192 was widely used for high-dose rate brachytherapy but at present Co-60 source emerges as more popular radioactive source for HDR-BT with longer half life, similar geometric and dosimetric properties. This represents a significant advantage over HDR Co-60 source by reduction of resource sparing, quality assurance and workload.
**Objective:** To determine acute toxicity and response of HDR C0-60 brachytherapy in cancer cervix patients
**Methods:** Fifty histological confirmed FIGO stage IB-IVA, cervical cancer patients received 50Gy/25Fr EBRT with concurrent weekly cisplatin for 5 weeks and 21 Gy in 3 fractions of HDR brachytherapy with Co-60 source using modified Fletcher suite applicator. ICRU-38 was used for treatment planning and dose optimization and response & toxicities were assessed by RECIST version-1.1 & CTCAE respectively. A total 3 months of follow up post RT was taken in study.
**Results:** The median EQD2and BED tumor (EBRT+HDR ICBT) was 80 Gy & 95.7 Gy while BED bladder and BED rectum was 100 Gy and 102.64 Gy respectively. Complete response at 3 months of follow up was 84%. Diarrhea grade $\leq$ 2 was present in 54% patients and only one patients developed grade 3 diarrhea. Proctitis grade $\leq$ 2 was present in 54% patients. Vomiting grade $\leq$ 2 was present in 12% patients while grade 1 urinary frequency and urgency was noted in more than 40% patients. All results were comparable with previously published studies.
**Conclusion:** Co-60 as HDR brachytherapy source is tolerable and is economical for low resource settings.



## INTRODUCTION

In India, cervical cancer accounts for almost 14% of all female cancer cases and second most common cancer in females.[1] Worldwide, Cancer cervix ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women. The global yearly incidence of cervical cancer for 2018 was 570000; the annual death rate was 311000.[2] Intracavitary brachytherapy (ICBT) and external beam radiotherapy (EBRT) is an essential component in curative treatment of cervical cancer and has a high therapeutic index by delivering a high dose to the tumour and lower dose to adjacent organ.[3] The important prognostic factors for cervical cancer are tumour volume, clinical stage, histology, age, and treatment modality.[4]

Cervical cancer is a highly curable disease. High dose rate (HDR) brachytherapy is now accepted standard treatment combined with external beam radiotherapy for cervical cancer. The specific advantage over low dose rate (LDR) brachytherapy is its convenience and applicability in out patient's basis. In past, the production of small source for HDR was possible only for iridium -192 sources .[5] However, the Ir-192 HDR system is costly due to its short half life, requiring frequently source change at 3 months intervals. Presently miniature Co-60 source is available with identical geometrical dimension to Ir-192. The advantage of miniaturized Co-60 source is due to its longer half life (5.26 years) ,requiring source replacement approximately every 5 years.[6] This represents a significant advantage from HDR Co-60 source by reduction of resource sparing ,quality assurance and workload. In carcinoma cervix, radiotherapy response is dose dependent,

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however risk of toxicity in normal tissues also increase with dose usage. The high energy of 1.25 MeV of Co-60 compared with 0.39 MeV of Ir-192 raises several concern about efficacy, toxicity, and quality of life of patients who are treated with Co-60 HDR brachytherapy.[7]

The objective of this study was to determine treatment outcome of HDR Co-60 brachytherapy in cancer cervix patients.

## METHODS & MATERIALS

The study includes a prospective analysis of 50 histological confirmed FIGO stage IB-IVA, cervical cancer patients treated with HDR- ICBT in a tertiary care centre of north- west India between May 2019 and April 2020. Patients with previous history of cervical irradiation or surgery, ECOG performance status ≤2, HIV sero positive and history of any co-morbidity were excluded from study population.

### *Method & Evaluation*

External beam radiotherapy (EBRT) was delivered to all patients by teletherapy cobalt -60 machine with dose 45-50 Gy in 25 fractions @ 180-200 per fraction over 5 days per week to gross disease and the potential subclinical disease. Antero-posterior and postero-anterior (AP/PA) fields were used. Concurrent weekly cisplatin was given as radiosensitizer on day 1or 2 of EBRT and given at least for 5 weeks.

Intracavitary brachytherapy was started after one week of completion of EBRT. All patients were treated by brachytherapy using modified Fletcher suite applicator. Total dose of 21 Gy was delivered in 3 session of one week apart. Each brachytherapy application was performed under conscious sedation. All patients were positioned in lithotomy position followed by antiseptic painting and draping and thorough pelvic vaginal examination was performed before each application.

The bladder was catheterized using a Foley catheter and Foley bulb was instilled with 7cc of diluted radio-opaque dye. The uterine cavity was sounded and a uterine tandem of appropriate length and angle with flange was inserted. Optimum ovoid were placed without compromising vaginal packing. Adequate vaginal packing was done anterior and posterior to the ovoid in an attempt to push the rectum and bladder away from high dose zone and rest of vaginal packing distally was done to stabilize the applicator. AP and lateral orthogonal films with help of jig (reconstruction box) were taken with C-arm X-ray machine and digital images were obtained. The orthogonal images were reconstructed and treatment planning was done with treatment planning system. ICRU-38 was used for treatment planning and dose optimization to point A, bladder, and rectum. A uniform dose of 7 Gy per fraction was used for all patients. The bladder point dose was kept to < 90 % of point A and rectal dose was kept up to <80 % of point A. Dwell position were optimized to minimize the dose to rectum and bladder points. EBRT and brachytherapy sessions were completed within 8 weeks. The response & acute toxicities of gastro-intestinal and genitor-urinary were assessed using Response Evaluation Criteria in Solid Tumours Criteria (Response Evaluation Criteria In Solid Tumours Version1.1 & Common Terminology Criteria for Adverse Events (CTCAE) respectively. All patients were assessed at the time of each application of HDR-ICBT and than subsequently 1st month, 2nd month and 3rd month after last session of ICBT.

## RESULTS

In this prospective study median age at presentation was 49.7 years with a range of 35-69 years. Majority of population was in 5th decade of life. Thirteen percent of the population Was having age less than 40 years. Moderately differentiated squamous cell carcinoma was the most common histological subtype with a frequency of 52%. In the present study, 72% patients were from rural background while 28% were from urban background, mostly having ECOG performance scale of 0 & 1 and hemoglobin level between 10-12 gm%. In FIGO Stage III (64%) was most common disease stage followed by stage II (30%). Patients' characteristics are shown in Table: 1.

**Table 1** Patient's characteristics

| Characteristics | N=50 | % |
|---|---|---|
| Age range | 35-69 | |
| Mean±SD | 49.69 ± .08 | - |
| ECOG score | | |
| 0 | 37 | 74% |
| 1 | 11 | 22% |
| 2 | 2 | 4% |
| Socioeconomic Status | | |
| Low | 33 | 66% |
| Middle | 17 | 34% |
| Background | | |
| Rural | 36 | 72% |
| Urban | 14 | 28% |
| FIGO stage | | |
| IB | 2 | 4% |
| II | 15 | 30% |
| III | 32 | 64% |
| IVA | 1 | 2% |
| Tumour size | | |
| <4 cm | 6 | 12% |
| >4 cm | 44 | 88% |
| Histopathology | | |
| WD SqCC | 21 | 42% |
| MD SqCC | 26 | 52% |
| PD SqCC | 3 | 6% |
| Hb level at baseline | | |
| >10gm% | 26 | 52% |
| <10 gm% | 24 | 48% |

A total of 21 Gy (BED-35.7Gy) was prescribed to point A in three applications. Total dose to bladder and rectum during HDR-ICBT applications was 15 Gy and 15.6 Gy respectively. EQD2 and BED tumour (EBRT+HDR ICBT) was 80 Gy & 95.7 Gy while BED bladder and BED rectum was 100 Gy and 102.64 Gy respectively.

In this study grade 1 vomiting was present in 8% patients while grade2 vomiting was present in 4% patients during treatment. Diarrhea grade ≤ 2 was present in 54% patents and only one patient developed grade 3 diarrhea. Proctitis grade ≤ 2 was present in 54% patients. Grade1 cystitis was present in 20 patients while grade 1 urinary frequency and urgency was noted in more than 40% patients. Acute toxicities of treatment are listed in Table: 3.

**Table 3** Acute toxicity of treatment

| Toxicity | Grade N (%) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Proctitis | 24 (48%) | 3 (6%) | 0 | 0 |
| Diarrhea | 21 (42%) | 6 (12%) | 1(2%) | 0 |
| Vomiting | 4 (8%) | 2 (4%) | 0 | 0 |
| Cystitis | 20 (40%) | 0 | 0 | 0 |
| Urinary frequency | 21 (42%) | 0 | 0 | 0 |
| Urinary urgency | 20 (40%) | 0 | 0 | 0 |

At 3 month of follow up 42 (84%) patients had complete response while partial response was present in 8(16%) patients. Treatment response is shown in table: 3.

**Table3** Response after 3 months of follow up

| Response after 3 months of follow up | |
|---|---|
| Complete response | 42 (84%) |
| Partial response | 8(16%) |

## DISCUSSION

The combination of external beam radiotherapy and brachytherapy gives high cure rate especially with concurrent use of platinum based chemotherapy with EBRT. Now HDR brachytherapy has been accepted as standard method of boost to primary disease after EBRT.

Iridium-192 is widely used as HDR source and is widely discussed in the literature. All the patients analyzed in present study received uniform radiation dose and the treatment parameters were selected to be of benefit to both early and locally advanced diseases as well as taking into consideration the possible associable normal tissue toxicities.

The total dose from both external beam and HDR brachytherapy in this study was 95.7 Gy BED of tumor while BED bladder and BED rectum was 100 Gy and 102.64 Gy respectively.

A $BED_{Gy10}$ between 86–109 has been shown to result in acceptable pelvic disease control rate[8] though for stage III disease, $BED_{Gy10} > 85$ was noted to be associated with higher local control and 5 year survival rates[9] than lower $BED_{Gy10}$. In a report by Chen *et al*[10] $BED_{Gy10}$ range between 82.6 and 101.1 (median 91.5) was associated with actuarial 5-year OS of 73% for stage 11B and 56% for stage III diseases and these rates were comparable with other studies with similar treatment parameters. In a similar study by Atara Ntekim *et al*.[7] median total BED ($Gy_{10}$) for tumour was 86.2 (84.4–88.8) while that for rectum (BED $Gy_3$) was 124.4 (120–133). Two patients (3%) had grade ≥2 GI toxicity while all others had grade ≤2 toxicity

In this study BED tumour was 95.7 Gy; however, complete response was 84% (Table: 2). Diarrhea grade ≤ 2 was present in 54% patents and only one patients developed grade 3 diarrhea. Proctitis grade ≤ 2 was present in 54% patients. Grade1 cystitis was present in 20 patients while grade 1 urinary frequency and urgency was noted in more than 40% patients. Grade ≤2 vomiting was present only in 6 patients (Table: 3).

Our study has shown that HDR with Co-60 radionuclide source well tolerated in cervical cancer patients. Only 1 patient (2%) had grade 3 diarrhea that necessitated the hospitalization and antibiotic therapy. There was no grade 3 or 4 acute genitourinary toxicity among the patients. The acute toxicity rates found in this study are similar when compared with those reported in studies using Ir-192 HDR radionuclide source. In literature, the reported rates of acute toxicity ≥ grade 3 ranged from 0%–8% for gastrointestinal and 0%–3% for genitourinary toxicities. Other studies with low –dose rate brachytherapy reported acute toxicity ≥ grade 3 from 0%–15% for gastrointestinal and 1%–8% for genitourinary toxicities.[7, 10-12]
The early (≤grade 2) gastrointestinal and genitourinary toxicities experienced by patients in this study are similar to outcomes from other studies though comparison is difficult because most authors ignore these mild symptoms hence they are not reported and if reported, consistent scoring criteria are not used (Table 4).
The acute genitourinary toxicity in this study is relatively low though the risk of late treatment related toxicity is yet to be evaluated but this, together with effectiveness of treatment, are expected to be similar to previous reports. In a retrospective analysis of Co-60 HDR ICBT in Iran, Mosalaei A. *et al*[13] reported a 10-year OS and DFS rate of 62.4% with about 6% severe genitourinary and/or gastrointestinal toxicity.

As this routine HDR ICBT practice in our centre with other studies are favourable, the use of adjusted treatment schedules with differential radiotherapy doses for early and late stage diseases as recommended by the American Brachytherapy Society and adopted in some earlier reports using Ir-192 HDR source[11,14] can be adopted for Co-60 radionuclide. In the adjustment treatment schedules, chemotherapy regimen is changed to weekly cisplatin with a dose of 30 $mg/m^2$, as this has been shown to be more tolerable and equally effective when compared with 40$mg/m^2$ or three weekly dosage.

**Table 4** Comparison of early acute toxicities in the previous studies

| Studies | Toxicities | | | | |
|---|---|---|---|---|---|
| | Proctitis | Diarrhea | Vomiting | Cystitis | Genitourinary |
| Chung *et al* 2005 | - | - | - | - | 22 |
| Chen *et al* 2006 | - | - | - | - | 5.7 |
| Shakespere *et al* 2006 | 4.8 | - | - | 23.8 | - |
| Atara Ntekim *et al* 2008 (Co-60) | 57 | 59 | 10 | 40 | 40 |
| Our study | 54 | 56 | 12 | 40 | 41 |

## CONCLUSION

This study shows that acute gastrointestinal and genitourinary toxicities following HDR-ICBT using Co-60 radionuclide source in treatment of cervical cancer is comparable with previously reported studies with Co-60 & Ir-192 HDR source brachytherapy. Cobalt 60 has lots of economic advantages over Ir-192 and hence suitable for low resource radiotherapy settings in developing countries.

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